REMARKS

I. PROSECUTION HISTORY

Applicants elected claims 26, 30, and 31 (Group VII) with traverse in response to a restriction requirement mailed May 17, 2002, in which the Office alleged that the claims as filed were directed to twelve distinct inventions. In an action mailed December 3, 2002, the Examiner maintained the restriction and rejected the elected claims 26, 30 and 31 on various grounds, and additionally presented objections relating to priority and the previously submitted Information Disclosure Statement.

II. EXPLANATION OF AMENDMENTS TO THE CLAIMS

A marked-up version of the changes made to the claims can be found in Appendix A hereto. Support for the amended and new claims is found throughout the specification.

New claim 38 finds support on pages 69-78 and on page 102 of the specification. New claim 39 finds support in section "(b)" of existing claim 30, and on page 14, lines 15-18, of the specification.

New claims 40-41 find support on pages 10-14 and 57-61 of the specification. More specifically, N-terminal deletion polypeptide mutants of amino acids 1-69 of SEQ ID NO: 2, in which 1-11 residues have been deleted finds support on page 11. A polypeptide having the amino acid sequence of SEQ ID NO: 25, which includes specified amino acid substitutions at various positions, finds support on pages 11-13, and 58-60. A polypeptide having the amino acid sequence of SEQ ID NOS: 30 "MDC (n+1)," SEQ ID NO: 31 "MDC-yl," or SEQ ID NO: 32 "MDC-eyfy" finds support on pages 13 and 58. N-terminal addition polypeptide mutants find support on page 13. MDCΔPro$_2$ polypeptides find support on pages 13 and 60.

New claims 42-43 finds support in claim 26, i.e. claim 26 as originally filed. Claim 42 finds further support on page 106, lines 1-7.

The present amendment introduces no new matter. As a convenience to the Examiner, the Applicants have set forth all pending claims in Appendix B. The Applicants do not intend by these or any other amendments to abandon the subject matter of any claim as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

III. THE RESTRICTION OF THE CLAIMS SHOULD BE REMOVED

In paragraphs 2 and 3, the Examiner maintained the restriction requirement, stating that the Applicants' arguments were not found persuasive. In maintaining the restriction, the Examiner alleged that Vicari's murine "TECK" protein was a murine "counterpart" to human MDC of the present application, and that the presence of Vicari's murine "TECK" as prior art meant that MDC could not serve as a special technical feature common to all the claims under PCT Rule 13.2. The present application discloses a murine Macrophage-Derived Chemokine "MDC" (SEQ ID NO: 36, *e.g.*, page 97), which has a sequence unlike that of the murine chemokine disclosed by Vicari. Because Vicari does not report murine MDC, as defined and disclosed in this application, restriction on the grounds that Vicari eliminates a special technical feature is improper.

In paragraph 4, the Examiner next alleged that the various restricted groups with specific discussion of groups IV, VII, VIII, and IX, were not related to a single general inventive concept under PCT Rule 13.1. This allegation is new. In the restriction requirement, the Examiner's allegation of a lack of a general inventive concept under Rule 13.2 was predicated on there allegedly being a lack of a common special technical feature. The present amendment, which is based on Rule 13.1 independent of Rule 13.2. is not proper as Rule 13.2 serves to define the test that must be used to evaluate Unity of Invention. Rule 13.2 states that Unity of Invention as defined under Rule 13.1 is fulfilled when the claims share a common "special technical feature." Groups IV, VII, VIII, and IX, along with all the other groups, all share MDC as a special technical feature. Accordingly, the Applicants request that the entire restriction requirement be removed.

Applicants explained in their Response to the restriction requirement that the claims of groups VII-X share a common special technical feature, namely, treating conditions in a mammal using a MDC antagonist. The Examiner has not specifically addressed that point.

IV. PRIORITY TO USSN 08/939,107 HAS BEEN PROPERLY ASSERTED

In paragraph 5, the Examiner asserted that the present application repeats a substantial portion of USSN 08/939,107 filed September 26, 1997, and suggested that Applicants claim priority thereto. The Applicants have already correctly claimed priority to said application as set out in the first paragraph following the title in the specification in accordance with M.P.E.P. § 201.11 (under "Reference to First Application") and 37 C.F.R. §

1.78(a)(2)(iii). In fact, the Applicants have claimed priority back to USSN 08/479,620, filed June 7, 1995. Clarification is requested if the Examiner believes that there is a defect in the priority claim.

V. THE INFORMATION DISCLOSURE STATEMENT HAS BEEN PROPERLY FILED

In paragraph 6, the Examiner asserted that the IDS filed April 30, 2002, and entered May 6, 2002, fails to comply with 37 C.F.R. § 1.98(a)(2), because copies of the references listed in the IDS had not been provided. The Applicants filed the IDS pursuant to 37 C.F.R. § 1.98(d), which does not require the Applicants to supply copies of references that were previously provided in a parent application. However, as a courtesy to the Examiner, the Applicants are providing with this response copies of those references that the Examiner has not yet considered. Because the IDS as filed was in compliance with the rules, consideration of the references without further fees is requested. A copy of the original 1449 Form is attached. In addition, a supplementary IDS and accompanying form SB/08A have been attached herewith for consideration by the examiner.

VI. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

In paragraph 8, the Examiner rejected claims 26, 30 and 31 as allegedly being indefinite under 35 U.S.C. § 112, second paragraph. The Applicants respectfully traverse.

A. "Amount Effective" is Definite and Clear When Viewed in the Context of the Claims and the Specification

The Examiner alleged that claim 26 is vague and indefinite because of the phrase "amount effective." An allergic reaction is manifested by specific symptoms understood by those of skill in the art, and disappearance or amelioration of those symptoms will be recognized by such persons as evidence that the allergic reaction has been palliated. Allergy symptoms that can be palliated include common symptoms recognized by physical examination and also manifestations that can be analyzed at the cellular level by determining if the MDC antagonist has inhibited the chemotaxis of eosinophils, neutrophils, or T_H2 cells. *See, e.g.,* page 108, lines 1-5, and page 106, lines 1-7. As with most fields of medicine, the amount effective to palliate will vary depending on the subject being treated and the type and the severity of allergic reaction, but is readily determined with routine dose-response studies and/or routine monitoring of patients' symptoms. The specification (Example 33) provides an exemplary dosing of an anti-MDC antibody of 0.1 to 5 mg/kg body weight, see page 107, line

29. Accordingly, the meaning of the phrase "amount effective" is both clear and definite when viewed by one of skill in the context of the claims and the specification. The rejection should be withdrawn.

B. The Indefiniteness Rejection of Claim 30 is Moot in Light of the Amendment

Second, the Examiner alleged that the metes and bounds of "a fragment or analog of" (as recited in claim 30) is indefinite, and that if the Applicants want to claim a particular fragment or analog that they would have to indicate the exact structure of the fragment or analog. Applicants respectfully disagree with the Examiner's position. If a claim that encompasses fragments and analogs appears broad to an examiner, that is not sufficient to warrant a rejection under § 112, second paragraph. *See* M.P.E.P. § 2173.04. The various specific fragments and analogs disclosed in the present application provide sufficient support for the original "fragment or analog" language. However, in order to expedite prosecution, claim 30 has been amended so as to omit the phrase "(a) a polypeptide fragment or analog of a vertebrate MDC that inhibits MDC activation." New claims 40 and 41 define specific antagonists by structure. Thus, with the amendment of claim 30 and addition of claims 40 and 41, the basis for the rejection is moot and should be withdrawn.

Applicants reserve the right to pursue claims to other fragments and analogs in related applications.

C. Recitation of "Capable of "Is Not Vague and Carries Patentable Weight As it Defines a Specific Characteristic of the Claimed Subject Matter

Third, the Examiner alleged that the use of the phrase "capable of" in claim 30 was vague and held no patentable weight, because the phrase allegedly describes a latent characteristic of a compound or composition. The Applicants dispute the "latent" characterization, because it is understood that a compound capable of binding to MDC binds to MDC. The terms are equivalent and define a specific characteristic of the claimed subject matter. Solely for the purpose of expediting prosecution and without narrowing the claim, the Applicants amend claim 30 to read in part "a polypeptide that specifically binds a vertebrate MDC polypeptide," rendering the rejection moot.

For the reason discussed above, the rejections of claims 26, 30 and 31 under 35 U.S.C. § 112, second paragraph should be withdrawn. Any rejection of new claims 38-43 would be improper for similar reasons.

VII. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN, BECAUSE THE SPECIFICATION IS ENABLING AS FILED

In paragraph 9, the Examiner rejected claims 26, 30 and 31 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. The Applicants respectfully traverse. No undue experimentation would be necessary to practice the invention for the reasons outlined below.

A. Published Studies Demonstrate That The Specification Is Enabling

The Examiner alleged that the art at the time of Applicants' invention was "nil," and with no demonstrative, unambiguous successes in treating allergic reactions in humans with either an MDC antagonist or a TARC antagonist. While such statements support a conclusion that the present invention is both novel and non-obvious, they do not support any conclusion about enablement. *See* M.P.E.P. § 2164.02, which cites *Gould v. Quigg*, 822 F.2d 1074, 1078, 3 U.S.P.Q.2d. 1302, 1304 where the Court held "The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting an application purporting to disclose how to do it." Data published subsequent to the filing of the present application demonstrates that the invention described in the specification as filed can be practiced successfully.

Example 33, beginning on page 107 of the specification describes an antigen-induced asthma/allergy model. A mammalian subject, e.g. a mouse, is given a substance such as ovalbumin to challenge the subject's immune system and elicit an allergic reaction. A known or putative MDC antagonist compound is then administered to the subject, and the subject is monitored to see if the compound is capable of palliating the allergic reaction. One way of assessing this capability is looking for a reduction in eosinophils and/or neutrophils in the lavage fluid (fluid taken from the respiratory tract, e.g. lungs, of the subject) in experimental subjects versus control subjects.

Since the present application was filed, a number of groups have published studies that demonstrate that the invention works as described in the application.

1. Gonzalo Demonstrates the Enabling Disclosure of the Present Application.

Gonzalo, *et al.*, *Mouse Monocyte-Dervived Chemokine is Involved in Airway Hyperactivity and Lung Inflammation*, J. Immunol., 163: 403-411 (1999) (hereinafter

Gonzalo or Appendix C) is attached as Appendix C.[1] Gonzalo used an anti-MDC antibody to suppress eosinophil recruitment in a mouse model of allergy. Gonzalo generated the allergic response with ovalbumin (OVA) (*see* page 404, first column), the same allergen taught in Example 33. Gonzalo's experimental mice were pretreated with the anti-MDC antibody, consistent with Example 33 (page 107, lines 26-29). A substantial reduction of eosinophils (page 407, second column, figure 4) occurred in the experimental mice. The ability of anti-MDC antibodies to decrease the number of eosinophils, as taught in the present application (page 108, lines 1 and 2), is demonstrated by comparing the results in figure 4B for Gonzalo's control (Rb Ig) mice that received a non-MDC antibody and experimental mice that received an anti-mMDC antibody This ability of anti-MDC antibodies is further demonstrated by the specific reduction of eosinophils in the lung interstitium, an area of the lung affected by the allergen, in figure 5. (*See* figures 4 and 5 on page 409, and discussion of the same.)

Accordingly, Gonzalo demonstrates that the invention as disclosed in the present application can be practiced effectively to palliate an allergic reaction.

2. Lloyd Demonstrates the Enabling Disclosure of the Present Application.

Lloyd, *et al.*, *CC Chemokine Receptor (CCR3)/Eotaxin is Followed by CCR4/Monocyte-Derived Chemokine in Mediating Pulmonary T Helper Lymphocyte Type 2 Recruitment after Serial Antigen Challenge In Vivo*, J. Exp. Med., 191: 265-73 (2000) (hereinafter Lloyd or Appendix D) describes a study similar to that in Gonzalo with ovalbumin-challenged mice treated with anti-MDC antibodies, i.e., "neutralizing Abs." (*See* page 269, column 2.) Inspection of figure 4A of Lloyd shows that anti-MDC antibodies decreased eosinophil migration by approximately two-thirds compared to control subjects. (*See* page 272 for figure 4, and page 270 for discussion thereof.) Like the results in Gonzalo, these results also comport with those stated in Example 33.

Accordingly, Lloyd demonstrates that the invention as disclosed in the present application can be practiced effectively to palliate an allergic reaction.

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[1] "Monocyte-Derived Chemokine" as used in Gonzalo is the same chemokine as "Macrophage-Derived Chemokine" of the present application.

3. Kawasaki Demonstrates the Enabling Disclosure of the Present Application.

Kawasaki, *et al.*, *Intervention of Thymus and Activation-Regulated Chemokine Attenuates the Development of Allergic Airway Inflammation and Hyperresponseiveness in Mice*, J. Immunol., 166: 2055-2062 (2001) (hereinafter Kawasaki or Appendix E) discloses an experimental study involving a mouse allergy model, in which anti-TARC antibodies are used to cause a dramatic decrease in the number of eosinophils. Kawasaki describes the methods used for the study including the use of ovalbumin as the allergen, and application of antibody prior to induction with the allergen. (page 2056, column 1.), which mirror the methods presented in Example 33. Kawasaki states: "Treatment with anti-TARC Ab strikingly decreased the total cell number and the number of eosinophils as well as lymphocytes recovered in the lavage fluid compared with those in the group treated with control Ab (Fig. 4)." (page 2058 and in figure 4 on page 2059.) A decrease in neutrophils is also reported (*see* figure 4) in agreement with Example 33 (specification, page 108, lines 1-2).

Accordingly, Kawasaki demonstrates that the invention as disclosed in the present application can be practiced effectively to palliate an allergic reaction.

4. Bochner et al. Support a Finding that the Specification is Enabling

In the rejection, the Examiner cited Bochner, *et al.*, J. Allergy Clin. Immunol. 103:527-32 (1999) for its teachings that MDC-induced chemotaxis of eosinophils is independent of CCR3 or CCR4. This report is entirely consistent with the patent application and does not support a rejection of any claim. (*See, e.g.*, the current application's Example 12, specifically page 62, lines 16-28.) The Bochner article merely confirms that MDC acts on eosinophils, and thus supports, rather than negates, patentability by supporting the conclusion that an MDC antagonist could inhibit MDC-induced chemotaxis of eosinophils.

5. Summary

The published studies cited by the Examiner and those provided in Appendices C, D and E, alone and in combination demonstrate that the claimed invention can be practiced successfully as described in the specification. Accordingly, the rejection of claims 26, 30 and, 31 under 35 U.S.C. § 112, first paragraph should be withdrawn.

B. The Level of Skill in the Art, the Examples and the Amount of Guidance Provided Indicate that the Specification Enables One of Skill to Perform the Full Scope of the Claimed Invention

The Examiner characterized the level of skill in the art as "high." The greater the knowledge in the art about the field of the invention, the less information needs to be explicitly stated in the specification. *See* M.P.E.P. § 2164.03. The specification of the present application provides detailed guidance regarding specific inhibitors, *see, e.g.*, page 12 of the specification, and to methods of using a MDC antagonist to palliate an allergic reaction in a mammalian host, *see, e.g.*, Example 33. The detailed instructions in the specification, combined with the high level of skill in the art, means that the specification is enabling.

The Examiner further characterized the Applicants' teaching as "limited," and relied on the disclosure in Example 30, which reports that monoclonal antibodies 252Y and 252Z inhibit CCR4-mediated cellular responses to MDC, to conclude that Applicants do not teach that any or all MDC antagonists or TARC antagonists are able to inhibit any or all allergic reactions in vivo or in vitro. The Examiner also alleged that the claims are too broad in respect to a method of treating an allergic reaction by using any or all MDC antagonists or TARC antagonists. The Applicants respectfully disagree.

The presence or absence of an example is not determinative on the issue of enablement, and an applicant need not describe all actual embodiments in order to have an enabling disclosure. *See* M.P.E.P. § 2164.02. Example 33, beginning on page 107 of the specification demonstrates how MDC antagonists and TARC antagonists can be tested and used to palliate an allergic reaction. Antibodies 252Y and 252Z, described in Examples 18 may be used according to the teachings of Example 33. Moreover, the Examiner admits on page 5 of the Office Action that "[t]he monoclonal antibodies against human MDC, 252Y, and 252Z inhibit CCR4 mediated cellular response to MDC in CCR4 transfected cell lines and block the antigen-induced asthma in an animal model." That admission alone supports allowance at least for claim 31 and new claim 38.

The Examiner also alleged that, because eosinophil accumulation is CCR4 or CCR3 independent, whether the use of CCR4 is able to block the MDC-induced eosinophil accumulation is questionable and lacks supporting evidence. Whether or not MDC or TARC affects eosinophil accumulation by binding or not binding to CCR4 or CCR3 does not prevent the use of CCR4 or a fragment thereof to bind to, and consequently antagonize the normal activity of, MDC or TARC, because such activity need not be dependent on binding

to either CCR4 or CCR3. The use of CCR4 (or a fragment thereof) in such a context is as an MDC or TARC inhibitor and is analogous to the use of an anti-MDC or anti-TARC antibody. Any inhibitor that binds MDC or TARC to prevent the MDC or TARC from binding a receptor would be expected to work, including CCR4 or a fragment thereof.

Accordingly, the rejection of claims 26, 30 and 31 under 35 U.S.C. § 112, first paragraph, should be withdrawn. Similarly, any rejection of new claims 38-43 under 35 U.S.C. § 112, first paragraph, would be improper.

VIII. THE REJECTIONS UNDER 35 U.S.C. § 102(B) SHOULD BE WITHDRAWN

In paragraphs 11 and 12, the Examiner rejected claims 26 and 30 under 35 U.S.C. § 102(b) as being anticipated by Wells, *et al.* (WO 96/23068A1). The Examiner alleged that Wells, *et al.* disclose a method for using a substance of CCR4, which has 100% homology to SEQ ID NO: 34 as it is claimed in the present application to treat an allergic condition. Specific reference was made to Wells, *et al.* at page 16 lines 3-11 and claims 1-5.

While Wells, *et al.* do report using CCR4 to screen for substances that could be useful in allergy treatments, Wells, *et al.* fail to teach or suggest using CCR4 itself or fragments thereof for treating allergies. Moreover, while Wells, *et al.* disclose the use of anti-CCR4 antibodies for purification of CCR4 and for diagnostic purposes (*see* page 10, lines 27-31 of Wells, *et al.*) they do not disclose using such antibodies for treating allergic symptoms or any other diseases or conditions.

Accordingly, Wells, *et al.* do not anticipate claims 26 and 30, and the rejection should be withdrawn. Any rejection of new claims 38-43 would be improper for similar reasons.

Moreover, when one of ordinary skill considers Wells in combination with Bouchner, one would question whether the CR4-modulating agents suggested by Wells would be effective for blocking MDC-induced allergic symptoms.

SUMMARY

In view of the remarks made above, Applicants request reconsideration of the claims. Applicants submit that all pending claims, after the entrance of this amendment, are in condition for allowance and request notification of the same.

Respectfully submitted,

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